Application No. 10/723,439 -- Winchell, inventor Examiner: Henley III, R.J.; Art Unit: 1614

Amendment No. 1 submitted in reply to Office Action of April 4, 2007

## Amendments to the Claims:

The following is a complete list of claims indicating the changes incorporated by the present amendment and replacing all prior versions of the claims. Any claims canceled herein and all deletions made in claims that are not canceled herein are done so without prejudice to being re-instituted at a later date in this or a related application.

## WHAT IS CLAIMED IS:

# Claim 1 (canceled)

Claim 2 (currently amended): A The pharmaceutical composition comprising (a) a complex of (i) a cyclic polyaza chelator having complexing affinity for first transition series elements and (ii) a cation of a member selected from the group consisting of calcium and magnesium and (b) a pharmacologically acceptable carrier, of claim 1 in which said cyclic polyaza chelator is a chelator having the formula

$$\begin{array}{c|c}
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wherein:

m, n, and p are each independently 2 or 3:

Application No. 10/723,439 -- Winchell, inventor Examiner: Henley III. R.J.: Art Unit: 1614

Amendment No. 1 submitted in reply to Office Action of April 4, 2007

q is 1 or 2;

R<sup>2</sup> and R<sup>3</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, hydroxyarylalkyl, and halogen-substituted versions thereof;

R1 is a member selected from the group consisting of R2, R2 and radicals of the formula:

$$\begin{array}{c|cccc}
R^{11} & R^{13} \\
C & C \\
R^{12} & R^{14}
\end{array}$$
(II)

wherein:

R<sup>11</sup>, R<sup>12</sup>, and R<sup>13</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, arylalkyl, alkoxy, alkylthio, alkenoxy, alkenylthio, aryloxy, arylthio, alkyl interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia, alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkenyl, aminoaryl, aminoarylalkyl, hydroxyalkyl, hydroxyalkyl, hydroxyarylalkyl, and halogen-substituted versions thereof;

R<sup>14</sup> is a member selected from the group consisting of H, hydroxy, amino, alkyl, alkyl interrupted by oxa, alkoxy, aryl, aryloxyalkyl, alkoxyaryl, alkoxyaryl, and halogen-substituted versions thereof.

r is zero or 1; and

X is a member-selected from the group consisting of alkyl, alkenyl, aryl,
arylalkyl, alkexy, alkylthie, alkenoxy, alkonylthie, aryloxy, arylthie, alkyl
interrupted by oxa, alkenyl interrupted by oxa, alkyl interrupted by thia.

Application No. 10/723,439 -- Winchell, inventor

Examiner: Henley III, R.J.; Art Unit: 1614

Amendment No. 1 submitted in reply to Office Action of April 4, 2007

alkenyl interrupted by thia, aryloxyalkyl, alkoxyaryl, aminoalkyl, aminoalkyl, aminoarylalkyl, hydroxyalkyl, hydroxyalkyl, hydroxyaryl, hydroxyaryl, hydroxyarylalkyl, halogen-substituted versions thereof, and radicals-selected form the group consisting of:

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Application No. 10/723,439 -- Winchell, inventor Examiner: Henley III, R.J.; Art Unit: 1614

Amendment No. 1 submitted in reply to Office Action of April 4, 2007

wherein.

R<sup>14</sup>, R<sup>13</sup> and R<sup>14</sup> are each independently as defined above;

R<sup>16</sup> and R<sup>17</sup> are each independently selected from the group consisting of

H. alkyl and aryl, or taken together form a ring structure:

R<sup>48</sup>-and R<sup>49</sup>-are each independently-selected from the group consisting of 
H, alkyl, aryl, alkoxy, alkyl interrupted by exa, arylexyalkyl, 
alkowaryl, and halogen-substituted versions thereofs

R<sup>20</sup>, R<sup>21</sup> and R<sup>22</sup> are each independently selected from the group consisting of II, alkyl, alkenyl, aryl, arylalkyl, alkeny, alkylthic, alkenyloxy, allkenylthic, aryloxy, aminoalkyl, aminoalkyl, aminoaryl, aminoarylakyl, hydroxyalkyl, hydroxyalkenyl, hydroxyaryl, and hydroxyarylalkyl, and

s is an integer of from 1 to 3.

and wherein, optionally, any two of  $R^1$ ,  $R^2$ , and  $R^3$  are combined to form a ring structure; and dimers of Formula I, said dimers being formed by the covalent attachment of two complexing agents of Formula I through a linking group having from 1 to 6 carbon atoms; and physiological salts thereof.

Claim 3 (original): The pharmaceutical composition of claim 2 wherein m, n, and p are each 2.

Claim 4 (original): The pharmaceutical composition of claim 2 wherein q is 1.

Claim 5 (original): The pharmaceutical composition of claim 2 wherein said cation is calcium.

Application No. 10/723,439 -- Winchell, inventor Examiner: Henley III, R.J.; Art Unit: 1614

Amendment No. 1 submitted in reply to Office Action of April 4, 2007

Claim 6 (original): The pharmaceutical composition of claim 2 wherein m, n, and p are each 2, q is 1, and said cation is calcium.

Claim 7 (original): The pharmaceutical composition of claim 2 wherein all alkyl are C<sub>1</sub>-C<sub>4</sub> alkyl.

Claim 8 (original): The pharmaceutical composition of claim 2 wherein all alkyl are C<sub>1</sub>-C<sub>4</sub> alkyl, all alkenyl are vinyl, all aryl are phenyl, all aralkyl are phenethyl or benzyl, all cycloalkyl are cyclopentyl or cyclohexyl, and all halogens are chlorine or fluorine.

Claim 9 (original): The pharmaceutical composition of claim 2 wherein  $R^2$  and  $R^3$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, and aralkyl.

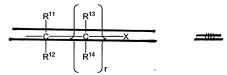
Claim 10 (original): The pharmaceutical composition of claim 2 wherein R<sup>2</sup> and R<sup>3</sup> are each independently selected from the group consisting of H and C<sub>1</sub>-C<sub>4</sub> alkyl.

Claim 11 (original): The pharmaceutical composition of claim 2 wherein R<sup>2</sup> and R<sup>3</sup> are each H.

Claim 12 (original): The pharmaceutical composition of claim 2 wherein  $\mathbb{R}^2$  and  $\mathbb{R}^3$  are each H and q is 1.

#### Claim 13 (canceled)

Claim 14 (currently amended): The pharmaceutical composition of claim 2 wherein  $\underline{q}$  is 1 and  $\underline{q}$  is  $1_{\overline{q}}$  said cation is calcium—and  $R^{\frac{1}{q}}$  is



Claims 15-17 (canceled)

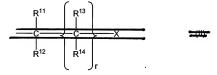
Application No. 10/723,439 -- Winchell, inventor Examiner: Henley III, R.J.; Art Unit: 1614

Amendment No. 1 submitted in reply to Office Action of April 4, 2007

Claim 18 (currently amended): The pharmaceutical composition of claim 2 47 wherein R<sup>16</sup> and R<sup>17</sup> are independently selected from the group consisting of H and C<sub>1</sub>-C<sub>4</sub> alkyl.

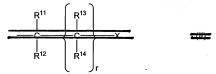
## Claims 19-20 (canceled)

Claim 21 (currently amended): The pharmaceutical composition of claim 2 wherein  $R^2$  and  $R^3$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, and aralkyl, and  $R^4$  is a member selected from the group consisting of H, alkyl, alkenyl, aryl, aralkyl, and



in which R<sup>11</sup>, R<sup>12</sup>, and R<sup>13</sup> are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, and arylalkyl, and R<sup>14</sup> is a member selected from the group consisting of H, hydroxy, amino, and alkyl.

Claim 22 (currently amended): The pharmaceutical composition of claim 2 wherein R+is



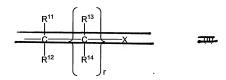
in which  $R^{11}$ ,  $R^{12}$ , and  $R^{13}$  are each independently selected from the group consisting of H, alkyl, alkenyl, aryl, and arylalkyl, and  $R^{14}$  is a member selected from the group consisting of H, hydroxy, amino, and alkyl.

Claim 23 (currently amended): The pharmaceutical composition of claim 2 wherein:

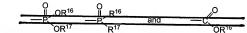
Application No. 10/723,439 -- Winchell, inventor Examiner: Henley III, R.J.; Art Unit: 1614

Amendment No. 1 submitted in reply to Office Action of April 4, 2007

## R+in



in-which  $R^{11}$ ,  $R^{12}$ , and  $R^{13}$  are each independently selected from the group consisting of H and  $C_1$ - $C_4$  alkyl,  $R^{14}$  is a member selected from the group consisting of H and  $C_1$ - $C_4$  alkyl, and X is a member-selected-from the group consisting of



in which R16 and R17 are each independently H or C1-C4 alkyl;

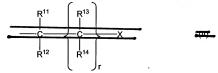
 $R^2$  and  $R^3$  are each independently selected from the group consisting of H and  $C_1$ - $C_4$  alkvl:

m, n, and p are each 2;

q is 1; and

said cation is calcium.

Claim 24 (currently amended): The pharmaceutical composition of claim 2 wherein R+is



in which R<sup>11</sup>, R<sup>12</sup>, and R<sup>13</sup> are each independently selected from the group consisting of H and C<sub>1</sub>-C<sub>4</sub> alkyl, and R<sup>14</sup> is a member selected from the group consisting of H and C<sub>1</sub>-C<sub>4</sub> alkyl.

Application No. 10/723,439 -- Winchell, inventor Examiner: Henley III, R.J.; Art Unit: 1614

Amendment No. 1 submitted in reply to Office Action of April 4, 2007

Claim 25 (original): The pharmaceutical composition of claim 2 wherein  $R^1$  is dihydroxyphosphorylmethyl,  $R^2$  is H, R is 2, n is 2, n is 2, n is 2, and q is 1.

Claim 26 (original): The pharmaceutical composition of claim 25 in which said cation is calcium.

### Claims 27-32 (canceled)

Claim 33 (currently amended): A method for mitigating ischemia or ischemia-reperfusion injury in a patient that has undergone cardiopulmonary bypass, said method comprising administering to said patient an effective amount of a pharmaceutical composition of claim 2.4.

Claim 34 (currently amended): A method for mitigating ischemia or ischemia-reperfusion injury in a patient that has undergone vascular surgery, said method comprising administering to said patient an effective amount of a pharmaceutical composition of claim 2 4.

Claim 35 (currently amended): A method for mitigating ischemia or ischemia-reperfusion injury in transplanted tissue in a patient that has undergone tissue transplant, said method comprising administering to said patient an effective amount of a pharmaceutical composition of claim 2 1.

Claim 36 (original): A method for providing neuroprotection or cardioprotection in a patient, said method comprising administering to said patient an effective amount of a pharmaceutical composition of claim 2.

Claim 37 (original): A method for enhancing the biological activity of a cyclic polyaza chelator having complexing affinity for first transition series elements, said method comprising administering said chelator as a pharmaceutical composition of claim 2.

Claim 38 (original): A method for mitigating ischemia or ischemia-reperfusion injury in a patient, said method comprising administering to said patient an effective amount of a pharmaceutical composition of claim 2.

Application No. 10/723,439 — Winchell, inventor Examiner: Henley III, R.J.; Art Unit: 1614

Amendment No. 1 submitted in reply to Office Action of April 4, 2007

Claim 39 (original): A method for mitigating damage to the central nervous system of a patient suffering from ischemic stroke, seizure or trauma, said method comprising administering to said patient an effective amount of a pharmaceutical composition of claim 2.

Claim 40 (original): A method for mitigating damage to the heart of a patient suffering a heart attack or arrhythmia, said method comprising administering to said patient an effective amount of a pharmaceutical composition of claim 2.

Claim 41 (original): A method for enhancing the biological activity of a cyclic polyaza chelator having complexing affinity for first transition series elements, said method comprising administering said chelator as a pharmaceutical composition of claim 23.

Claim 42 (original): A method for mitigating ischemia or ischemia-reperfusion injury in a patient, said method comprising administering to said patient an effective amount of a pharmaceutical composition of claim 23.

Claim 43 (original): A method for providing neuroprotection or cardioprotection in a patient, said method comprising administering to said patient an effective amount of a pharmaceutical composition of claim 23.

Claim 44 (original): A method for mitigating damage to the central nervous system of a patient suffering from ischemic stroke, seizure or trauma, said method comprising administering to said patient an effective amount of a pharmaceutical composition of claim 23.

Claim 45 (original): A method for mitigating damage to the heart of a patient suffering a heart attack or arrhythmia, said method comprising administering to said patient an effective amount of a pharmaceutical composition of claim 23.

Claim 46 (original): A method for enhancing the biological activity of a cyclic polyaza chelator having complexing affinity for first transition series elements, said method comprising administering said chelator as a pharmaceutical composition of claim 25.

Application No. 10/723,439 -- Winchell, inventor Examiner: Henley III, R.J.; Art Unit: 1614

Amendment No. 1 submitted in reply to Office Action of April 4, 2007

Claim 47 (original): A method for mitigating ischemia or ischemia-reperfusion injury in a patient, said method comprising administering to said patient an effective amount of a pharmaceutical composition of claim 25.

Claim 48 (original): A method for providing neuroprotection or cardioprotection in a patient, said method comprising administering to said patient an effective amount of a pharmaceutical composition of claim 25.

Claim 49 (original): A method for mitigating damage to the central nervous system of a patient suffering from ischemic stroke, seizure or trauma, said method comprising administering to said patient an effective amount of a pharmaceutical composition of claim 25.

Claim 50 (original): A method for mitigating damage to the heart of a patient suffering a heart attack or arrhythmia, said method comprising administering to said patient an effective amount of a pharmaceutical composition of claim 25.